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Migraine preventive therapy: current and emerging treatment options

Abstract In this paper we review new treatment options for migraine prevention. We start with an overview about migraine and then briefly discuss current indications for migraine prevention and new and emerging preventive medications.

Key words Migraine prevention · Migraine prophylaxis · Migraine treatment

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Introduction

Migraine is a chronic neurological disease characterised by episodic attacks of headache and associated symptoms. In Western countries, the condition affects 11% of the adult population [1]. Migraine is a heterogeneous condition that results in a range of symptom profiles and various degrees of disability both within and among different individuals [2]. The disability caused by migraine can be severe and imposes a considerable burden on the sufferer and society [3–5]. In this paper we review new treatment options for migraine prevention. We start with an overview about migraine pathophysiology and then briefly discuss current indications for migraine prevention and new and upcoming preventive medications. Because we focus on new medications, some of the data we present herein were acquired in well designed double-blind, controlled studies, while the efficacy of other drugs is supported only by open, uncontrolled trials (noted in the text wherever appropriate).

Principles of migraine prevention

Migraine pharmacotherapy is usually divided into two categories: drugs that are taken daily whether or not headache is present to reduce the frequency, duration and severity of attacks (preventive therapy) and drugs that are taken acutely to stop attacks (acute care therapy) [6, 7]. The US Headache Consortium Guidelines [8, 9] suggest that preventive treatment should be considered in the following circumstances:

- recurring migraine that significantly interferes with the patient's daily routine despite acute treatment (e.g., two or more attacks a month that produce disability that

lasts ≥3 days, or headache attacks that are infrequent but produce profound disability);
- failure of, contraindication to, or troublesome side effects from acute medications;
- overuse of acute medications;
- special circumstances, such as hemiplegic or basilar migraine or attacks with a risk of permanent neurological injury;
- very frequent headaches (more than two a week), or a pattern of increasing attacks over time, with the risk of developing rebound headache with acute attack medicines;
- patient preference, i.e., the desire to have as few acute attacks as possible.

It is not clear how preventive therapy works, although it seem likely that it modifies the sensitivity of the brain that underlies migraine [10].

Medications from a broad range of classes have demonstrated efficacy in preventing migraine. Clinicians are most familiar with the data supporting use of β-adrenergic blockers, antidepressants, calcium-channel antagonists and valproate [10]. Some of these effective agents were discovered serendipitously after use for other purposes and still represent the majority of prescriptions written for migraine prevention. Because most of them are considered standard preventive medications, they will not be discussed.

Some of the available options are listed in Table 1, and the evidence regarding their use has been extensively reviewed (Table 2) [9]. When deciding to initiate preventive pharmacotherapy, several general principles of management may prove helpful:

Begin the preventive medications at a low dose and gradually increase the dose over weeks or months if necessary. For example, if no side effects emerge and if the desired clinical response has not yet been achieved, and the ceiling dose for the drug has not been reached, the dose can be escalated.

Manage the patient's expectations regarding the time and extent of clinical benefit. Many preventive medications take a minimum of 3 or 4 weeks for a therapeutic response at a particular dose; patients need to be patient and compliant with the agreed-upon treatment plan. Two thirds of the patients given any of the drugs listed in Table 3 will have a 50% reduction in the frequency of headaches. Breakthrough headaches are inevitable and must be managed with acute treatment. It is important to explain the side effects of these drugs and engage the patient in the decision-making process.

Establish a comprehensive migraine management plan that includes long-term goals, tips on when the medication needs to be changed, a regular office visit schedule and specific information on adverse reactions that may warrant discontinuing the medication, returning to the clinic, calling the office or even going to the hospital on an emergency basis.

Table 1 Selected preventive therapies for migraine

Generic treatment	Doses
Alpha2-agonists	
Clonidine tablets	0.05–0.3 mg/day
Guanfacine tablets	1 mg
Anticonvulsants	
Divalproex sodium tablets*	500–1500 mg/day
Gabapentin tablets*	300–3000 mg
Levetiracetam tablets	1500–3000 mg
Topiramate tablets*	50–400 mg
Zonisamide capsules	100–400 mg
Antidepressants	
MAOIs	
Phenelzine tablets	30–90 mg/day
TCA	
Amitriptyline tablets*	30–150 mg
Nortriptyline tablets	30–100 mg
SSRIs	
Fluoxetine tablets	10–40 mg
Sertraline tablets	25–100 mg
Paroxetine tablets	10–30 mg
Venlafaxine tablets	37.5–225 mg
Mirtazapine tablets	15–45 mg
Beta-blockers	
Atenolol tablets*	25–100 mg
Metoprolol tablets	50–200 mg
Nadolol tablets	20–200 mg
Propranolol tablets*	30–240 mg
Timolol tablets*	10–30 mg
Calcium channel antagonists	
Verapamil tablets*	120–480 mg
Nimodipine tablets	30 mg tid
Diltiazem tablets	30–60 mg tid
Nisoldipine tablets	10–40 mg qd
Amlodipine tablets	2.5–10 mg qd
NSAIDs for prevention	
Naproxen sodium tablets*	500–1100 mg/day
Ketoprofen tablets	150 mg/day
Mefanamic acid tablets	1500 mg/day
Flurbiprofen tablets	200 mg/day
Anti-serotonergic agents	
Methysergide tablets*	2–12 mg
Cyproheptadine tablets	2–16 mg
Pizotifen tablets*	1.5–3 mg
Miscellaneous	
Montelukast sodium tablets	5–20 mg
Lisinopril tablets	10–40 mg
Candesartan	8–32 mg/day
Botulinum toxin A injection	25–100 units (IM)
Feverfew tablets	50–82 mg/day
Magnesium gluconate tablets	400–600 mg/day
Riboflavin tablets	400 mg/day
Petasites 75 mg*	75 mg bid
Coenzyme Q10	300 mg/day

*Evidence for moderate efficacy from at least two well designed placebo-controlled trials

Table 2 Choices of preventive treatment in migraine

Drug	Efficacy	Adverse events	Comorbid condition	
			Relative contraindication	Relative indication
Beta-blockers	4+	2+	Asthma, depression, congestive heart failure, Raynaud's disease, diabetes	Hypertension, angina
Antiserotonin				
Pizotifen	4+	2+	Obesity	
Methysergide	4+	4+	Angina, vascular disease	Orthostatic hypotension
Ca channel blockers				
Verapamil	2+	1+	Constipation, hypotension	Aura, hypertension, angina, asthma
Flunarizine	4+	2+	Parkinson's, depression	Dizziness, vertigo
Antidepressants				
TCAs	4+	2+	Mania, urinal retention, heart block	Depression, anxiety, insomnia, pain
SSRIs	2+	1+	Mania	Depression, OCD
MAOIs	4+	4+	Unreliable patient	Refractory depression
Anticonvulsants				
Divalproex/valproate	4+	2+	Liver disease, bleeding disorders	Mania, epilepsy, anxiety
Gabapentin	2+	2+	Liver disease, bleeding disorders	Mania, epilepsy, anxiety
Topiramate	4+	2+	Kidney stones	Mania, epilepsy, anxiety
NSAIDs	2+	2+	Ulcer disease, gastritis	Arthritis, other pain disorders

*Ratings are on a scale from 1+ (lowest) to 4+ (highest) based on strength of evidence. From reference [34], with permission

Table 3 Efficacy of levetiracetam in the preventive treatment of refractory transformed migraine

Endpoint	Baseline	3 months	*p* value
Headache frequency	24.9	18.0	<0.001
Moderate or severe headache	16.8	11.7	<0.01
MIDAS scores	62.8	40.8	=0.01
HIT scores	63.4	59.4	<0.01

Evidence regarding the preventive drugs is most available for the beta-blockers, antidepressants, calcium channel antagonists and anti-epileptic agents. We will briefly discuss these classes of drugs below.

Beta-blockers

The AHCPR Technical Report analysed 74 controlled trials of beta-blockers for migraine prevention [9]. Propranolol, nadolol, atenolol, metoprolol and timolol have been shown to be effective. The beta-blockers that are partial agonists and have intrinsic sympathomimetic activity have not been found to be effective for the prevention of migraine. As the relative efficacy of the different beta-blockers has not been clearly established, choice should be made based on beta-selectivity, convenience of drug formulation, adverse events (AEs) and the patient's individual reaction to a specific drug. Because beta-blockers can produce behavioural side effects such as drowsiness, fatigue, lethargy, sleep disorders, nightmares, depression, memory disturbance and hallucinations, they are best avoided in patients with depression. Decreased exercise tolerance limits their use by athletes. Less common side effects include impotence, orthostatic hypotension, significant bradycardia and aggravation of intrinsic muscle disease. Beta-blockers are especially useful for patients with comorbid angina or hypertension. They are relatively contraindicated for patients with congestive heart failure, asthma, Raynaud's disease and insulin-dependent diabetes.

Antidepressants

The currently available antidepressants consist of a number of different classes of drugs with different mechanisms of action. The tricyclic antidepressants (TCAs) most commonly used for migraine prevention include amitriptyline, nortriptyline, doxepin and protriptyline. Amitriptyline is the only antidepressant with fairly consistent support for its efficacy in migraine prevention. Other agents have not been rigorously evaluated; their use is based largely on clinical experience and uncontrolled reports [9]. Many headache experts use nortriptyline in preference to amitriptyline because of its more favourable AE profile. TCAs are better used for patients who have sleep disturbance or comorbid depression. Serotonin specific reuptake inhibitors (SSRIs), such as fluoxetine, paroxetine and sertraline, can be used to treat coexistent depression, based on their favourable side-effect profiles; their efficacy as migraine preventives has not been established and they may increase migraine. Side effects from TCAs are common. Most involve anti-muscarinic effects, such as dry mouth and sedation. The drugs also cause increased appetite and weight gain; cardiac toxicity and orthostatic hypotension occur occasionally. Other classes of antidepressants such as serotonin norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine and duloxetine, as well as the miscellaneous ones such as bupriprion, have not been well studied.

Calcium-channel blockers

The AHCPR Technical Report identified 45 controlled trials of calcium antagonists [9]. A meta-analysis supports the clinical benefits of flunarazine (not available in the USA). Nimodipine had mixed results in placebo-controlled trials. The evidence for nifedipine was difficult to interpret. We avoid it as it is a significant vasodilator and may worsen migraine attacks. Verapamil was more effective than placebo in two of three trials, but both positive trials had high dropout rates. Of the calcium-channel blockers available in the USA, verapamil is the most widely used. Verapamil is especially useful for patients with comorbid hypertension or with contraindications to beta-blockers, such as asthma and Raynaud's disease. Calcium-channel blockers are also useful for patients who have migraine with prolonged aura or hemiplegia. Constipation and oedema are verapamil's most common AEs.

Antiepileptic drugs

Antiepileptic drugs (AEDs) are increasingly recommended for migraine prevention because of placebo-controlled, double-blind trials that prove them effective [9, 12–17]. Valproate or divalproex, topiramate and gabapentin have demonstrated efficacy [18].

Many patients find divalproex sodium to be effective at a low dose (500–1000 mg/day). Side effects include sedation, hair loss, tremor and changes in cognitive performance. Nausea, vomiting and indigestion can occur, but these are self-limited side effects. Hepatotoxicity is the most serious side effect, but irreversible hepatic dysfunction is extremely rare in adults. Pancreatitis has also been reported. Baseline liver function studies should be obtained, but routine follow-up studies are probably not routinely needed in adults on monotherapy. Young females seem to develop ovarian dysfunction at a higher rate than those on other AEDs. Patient follow-up is necessary to adjust the dose and monitor side effects.

Gabapentin (1800–2400 mg) was found to be superior to placebo in reducing the frequency of migraine attacks in a controlled, double-blind trial, supporting the results of previous open-trials. The responder rate was 36% for gabapentin and 14% for placebo [19]. The most common AEs were dizziness and drowsiness. Relatively high patient withdrawal rates due to AEs were reported in some trials.

Topiramate is a structurally unique anticonvulsant with rapid and almost complete oral absorption. Topiramate is either weight neutral or has been associated with weight loss, not weight gain (a common reason to discontinue preventive medication) with chronic use. Topiramate should be started at a dose of 15–25 mg/day at bedtime and increased weekly to 100–200 mg/day in divided doses. AEs include weight loss, paraesthesias and cognitive dysfunction (which is often prevented by slow gradual dose escalation). Topiramate should be used with caution in patients who have a history of renal calculi. A recent double-blind controlled study showed that topiramate is superior to placebo in the preventive treatment of migraine, supporting several previous open-label trials [20].

AEDs are especially useful when migraine occurs in patients with comorbid epilepsy, anxiety disorder or bipolar illness. They can be safely administered to patients with depression, Raynaud's disease, asthma and diabetes, circumventing the contraindications to beta-blockers. With the exception of valproic acid, many AEDs may interfere with the efficacy of oral contraceptives. Caution is therefore advised in women on AEDs and oral contraceptives. Topiramate occasionally causes breakthrough bleeding.

New options in migraine prevention

Levetiracetam

Levetiracetam (LTC) is a new anticonvulsant with an unknown mechanism of action. Its efficacy in migraine prevention may be related to a possible effect on cortical

spreading depression (CSD), which is an early pathophysiological process in a migrainous attack.

Open trials have shown the efficacy of LTC in the treatment of refractory migraine [21]. In an open study, Drake et al. [22] studied 10 patients with migraine with aura, 40 with migraine without aura and 12 patients suffering from daily headache. Other preventive and abortive medications were continued. There was a statistically significant decrease in headache frequency and severity after the first month.

A recent study performed at The New England Center for Headache in Stamford, CT, USA assessed the efficacy of LTC in the preventive treatment of refractory transformed migraine. Baseline data was collected from 35 subjects. Our ITT population consisted of 30 subjects (73.3% females, mean age of 46.5 years). A total of 9 (30%) subjects were not using other preventive drugs when included, 6 (20%) were using one preventive drug and 15 (50%) were using two or three preventive drugs. Median headache frequency per month at baseline was 24.9 (4.6) and a significant reduction of headache frequency was obtained in 1 month (19.4, $p<0.001$), 2 months (18.4, $p<0.001$) and 3 months (18.0, $p<0.001$) (Table 2). At baseline, the mean number of moderate or severe days was 16.8, compared to 13.2 after 1 month (NS). Significance was reached after 2 months (11.9, $p<0.01$) and 3 months (11.7, $p<0.01$). The mean MIDAS scores were significantly reduced at 3 months, compared to baseline (40.8 *vs.* 62.8, $p=0.01$). Mean HIT scores at baseline were 63.4, compared to 59.4 after 3 months ($p<0.01$). Fifteen (50%) patients reported side effects and, considering the ITT population, 5 (16.7%) dropped out of the study because of side effects. No serious AEs were reported [23].

LTC can be started at 250 mg at night and increased by 250 mg each week. Some physicians start at 500 mg hs and move up by 500 mg each week. Minimally effective doses appear to be 1500 mg and most patients need 2000–2500 mg/day with few AEs.

The side effects of LTC reported in initial clinical trials for epilepsy occurred in at least 3% of the patients and presented as fatigue or tiredness, somnolence, dizziness and infection (common cold or upper respiratory tract infection).

Zonisamide

Zonisamide (ZNS) is a sulphonamide derivative, chemically and structurally unrelated to other anti-epileptic drugs, recently introduced into the USA. It has been available in Japan and in Korea for over 10 years where it was usually indicated as an adjunctive therapy for partial seizures. Two open studies of ZNS in the treatment of refractory migraine were recently presented as abstracts showing its efficacy, especially regarding headache intensity and frequency [10, 24]. The first trial included 34 migraine patients who were resistant to other preventive treatments. ZNS was started in a dose of 100 mg/day and titrated, as tolerated, to 400 mg/day. The headache severity was significantly reduced but figures were not presented [24]. In the second study, 37 patients with refractory migraine and mixed headache syndromes were investigated. All had failed to respond to at least two preventive, but not specified, agents before. When the poster was presented 27 patients had already been evaluated and 14 patients revealed decreasing headache frequency [10]. Considering the fact that these studies involved very difficult to treat headache patients, these data support the potential utility of ZNS in the treatment of refractory migraine overall, although controlled studies are still lacking. The side effects reported in these studies were paraesthesias, fatigue, anxiety and weight loss. Agitated dysphoria and difficulty concentrating were also observed.

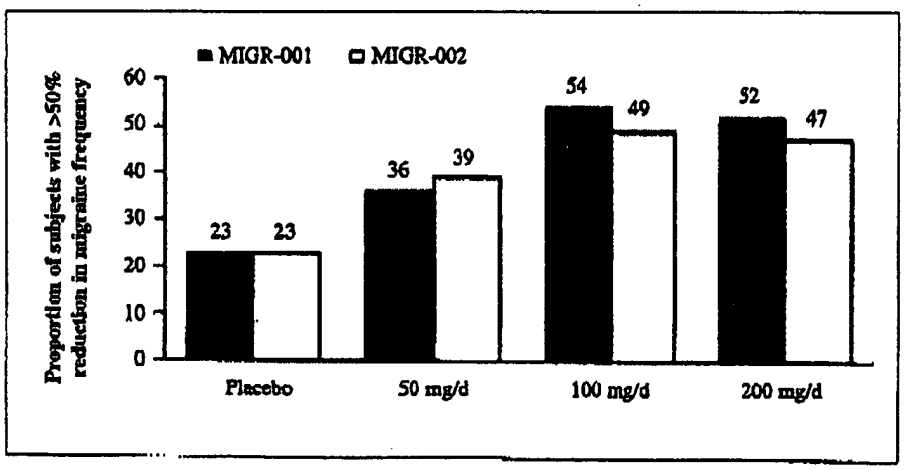

Fig. 1 Efficacy of topiramate in the preventive treatment of migraine (from reference [31], modified)

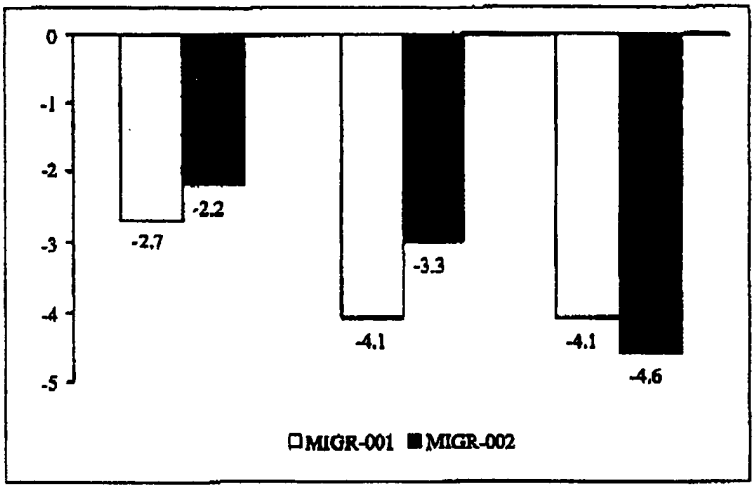

Fig. 2 Weight loss in participants of two clinical trials of topiramate in the prevention of migraine

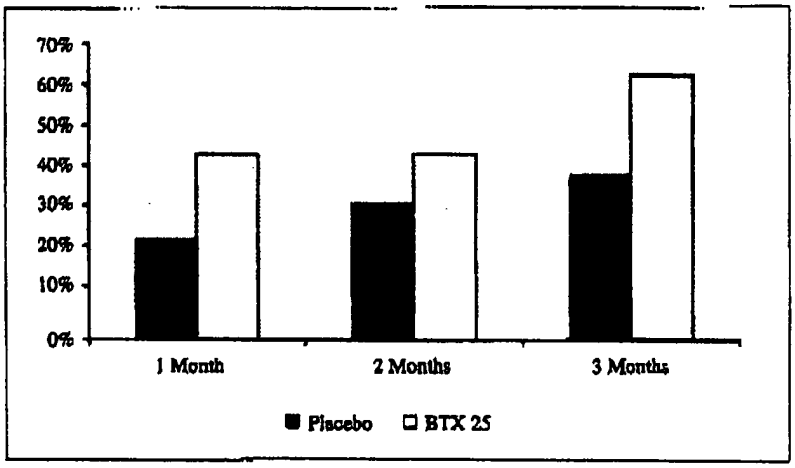

Fig. 3 Percentage of subjects with at least a decrease of two headaches in the frequency of their migraines (after reference [42]), $p<0.05$ at 3 months

Botulinum toxin (BTX)

BTX type-A injections often reduce the pain associated with conditions such as cervical dystonia, achalasia, rectal fissures and myofascial pain syndrome. BTX-A has been approved in the USA for blepharospasm and recently for forehead wrinkles. Some open-label, non-controlled studies of BTX-A suggested benefits for patients with migraine and tension-type headache [25–27].

BTX is a potent toxin that causes muscle paralysis when found pathologically. However, current migraine pathophysiological theories do not consider muscular factors as prominent. Recently, antinociceptive effects of BTX have been postulated. A study using rat trigeminal ganglion neurons demonstrated that BTX type A can directly decrease the amount of calcitonin gene-related peptide (CGRP) released from trigeminal neurons. The authors suggest that the efficacy of BTX-A may be at least partially explained by this mechanism as well as its direct effect on muscles [28]. Other studies have shown its effect in decreasing peripheral production of glutamate and substance P.

A recent double-blind study, evaluating 25 Units (25-U) and 75-U doses showed that, compared with vehicle treatment, subjects in the 25-U BTX type-A treatment group had significantly fewer migraine attacks per month, a reduced maximum severity of migraine pain, a reduced number of days using acute care migraine medications and reduced incidence of migraine-associated vomiting (Fig. 3). Those in the 75-U group were not significantly better than placebo [29].

A study assessing the efficacy of BTX-A in 100 patients with refractory headaches (migraine and chronic daily headaches) showed a statistically significant reduction of the frequency of headache days 1 month after BTX-A was administered (28.2 days *vs.* 14.2 days at the baseline, $p<0.001$), which was maintained through the three months of study; similarly, a significant reduction in the headache index (40.3 *vs.* 22.3, $p<0.001$) and number of severe days with headache per month (74.9 *vs.* 2.6,

$p<0.001$) were found at 1 month and maintained through the 3 months of study. MIDAS scores were reduced from 34.5 at baseline to 15.9 at 3 months ($p<0.001$) [30].

A typical treatment protocol is to inject BTX symmetrically into glabellar, frontalis and temporalis muscles and, if pain is present, also into pericranial and paracervical regions. The major side effect, avoidable with proper placement, is mild ptosis that usually lasts less than one week. Injections can be repeated every 3–4 months if patients have a beneficial effect, which wears off after 3–4 months post-treatment. Standard protocols tend to use 60–100 U in multiple sites from the forehead to the cervical muscles and note that patients often need repeat treatment in 3–4 months [31]. Some clinicians use higher doses. Side effects are usually mild and transient and include frontal weakness, ptosis (in migraine trials other kinds of weakness are infrequently reported) and pain in the sites of injections.

Tizanidine

Tizanidine (TZN) is a centrally acting, pre-synaptic alpha-2 adrenergic agonist only recently studied for use in headache patients. Its mechanism of action is thought to be through a decrease of norepinephrine release from the locus coeruleus in the upper, dorsal pons of the brainstem [32]. In a pilot open-label study, TZN was administered to 39 patients with more than 15 headache days per month. Thirty-one patients completed 12 weeks of treatment with an average of 14 mg/day (divided over three daily dosages). The overall headache index (frequency x average intensity x duration) declined significantly ($p<0.00000002$). Mild-to-moderate AEs, such as somnolence, asthenia and dry mouth were reported by more than 10% of the patients but only three discontinued treatment due to AEs [33]. A recent double-blind, multicentre study including 134 chronic daily headache patients who were randomised either to TZN or placebo found the following results after one month of utilisation of TZN: mean reduction in the total headache days of 30% *vs.* 22% for the placebo group; mean reduction of 55% in the number of days with severe pain *vs.* 21%; and mean reduction in the headache index of 54% *vs.* 19%. The mean dosage used was 18 mg/day (range 2–24, SD 6.4, median 20) divided equally over three dose intervals/day. AEs were also reported by >10% of the patients and presented as somnolence (47%), dizziness (24%), dry mouth (23%) and asthenia (19%). Dropouts due to AEs did not differ significantly between TZN and placebo [34].

Nefazodone

Nefazodone hydrochloride is a phenylpiperazine antidepressant with a distinct and atypical mechanism of action. It is a potent, selective 5-HT_2 antagonist that moderately blocks serotonin and noradrenaline/norepinephrine reuptake, with minimal affinity for cholinergic, histaminic or alpha-adrenergic receptors. Nefazodone has been shown to be an effective antidepressant with similar efficacy to other antidepressants. The potency and specificity of its 5-HT_2 antagonism suggests that nefazodone might be particularly effective in the prophylactic treatment of CDH [18].

A recent open-label study involving 52 patients with CM treated with nefazodone (median dose 300 mg/day) for 12 weeks revealed significant improvement for all headache diary measures [18]. During the last month of treatment, 71% of the patients completing the study showed at least a 50% reduction in headache index compared to baseline, and 59% had at least a 75% improvement. Significant improvements were also seen in pain disability index, quality of life and depression. Common mild to moderate AEs reported by 10% or more of the patients included fatigue, nausea, dry mouth, dizziness, sleep disturbance, blurred vision, irritability/nervousness and sedation. These results provide preliminary support for the efficacy of nefazodone in the prophylaxis of CDH, which might be followed by randomised, double-blind controlled studies. It is important to note that it is metabolised by CYP450 3A4 and patients on it cannot be given eletriptan.

Lisinopril

Lisinopril (LSN) is an angiotensin-converting enzyme (ACE) inhibitor frequently used to treat hypertension and heart failure. It is structurally related to enalapril and does not have an indication for the prevention of migraine, although it possesses various pharmacological effects that may be relevant in the pathophysiology of migraine. It blocks the conversion of angiotensin I to angiotensin II, it also alters sympathetic function, inhibits free radical activity and blocks degradation of bradykinin, encephalin and substance P [35]. LSN has a clear potential to migraine prophylaxis because migraineurs present more commonly the ACE DD gene, which codes for a higher ACE activity [19]. LSN was studied in a double-blind, placebo-controlled, crossover trial for the preventive treatment of migraine in 60 patients. The dose used was 20 mg/day divided over two doses and among the 47 patients who completed the study, the decrease of the endpoints hours with headache, days with headache, days with migraine, index of headache severity and doses of symptomatic medications used was moderate (approximately 20%) but significantly different from placebo. The main side effects are cough, hypotension and fatigue. The oral doses of LSN for use in hypertension range from 5 to 40 mg daily (in single or divided doses), with 10 mg daily as appropriate for the initiation of therapy.

Candesartan

A recent double-blind, placebo-controlled crossover study performed in a Norwegian neurological outpatient clinic assessed the efficacy of angiotensin II receptor blocker Candesartan (CST) in the prevention of migraine. Sixty patients went through a placebo run-in period of 4 weeks, followed by two 12-week treatment periods separated by 4 weeks of placebo washout. Thirty patients were randomly assigned to receive one 16-mg CST cilexetil tablet daily in the first treatment period followed by 1 placebo tablet daily in the second period. The remaining 30 received placebo followed by CST. After 12 weeks, the mean number of days with headache was 18.5 with placebo *vs.* 13.6 with CST (p=0.001) in the intention-to-treat analysis (n=57). Some secondary endpoints also favoured CST, including hours with headache (139 *vs.* 95; p<0.001), days with migraine (12.6 *vs.* 9.0; p<0.001), hours with migraine (92.2 *vs.* 59.4; p<0.001), headache severity index (293 *vs.* 191; p<0.001), level of disability (20.6 *vs.* 14.1; p<0.001) and days of sick leave (3.9 *vs.* 1.4; p=0.01), although there were no significant differences in health-related quality of life. The number of CST responders (≥50% response compared to placebo) was 18 (31.6%) of 57 for days with headache and 23 (40.4%) of 57 for days with migraine. AEs were mild and infrequent [20].

Carabersat

Carabersat (CBS) is a new anticonvulsant devoid of cardiovascular side effects with minimal CNS adverse actions, which opens the ATP-sensitive K^+ channels [36]. It has a potential action in preventing migraine as it acts through an inhibition of CSD in cats as well as trigeminal nerve-induced vasodilatation. Its good therapeutic index and the markedly reduced neurological impairments could make it a useful agent for migraine prophylaxis pending efficacy parameters of controlled studies that are underway.

Petasites

Petasites (PTS) is an extract from the plant *Petasites hybridus* (butterbur) found throughout Europe and parts of Asia, which has been used for medicinal purposes for centuries. This compound has been marketed in Germany for migraine and seems to act through calcium channel regulation and inhibition of peptide-leukotriene biosynthesis [37]. Two studies have analysed the possible efficacy of PTS in migraine prophylaxis. The first was a randomised, double-blind, placebo-controlled trial with 50 mg twice daily, which significantly reduced the number of migraine attacks and migraine days per month [38]. Recently another study conducted by Lipton et al. [39] enrolled 245 patients in a 5-month study who received either 50 mg, 75 mg or placebo twice daily. The 4-month mean attack count was reduced by 48% in patients who received 75 mg twice daily while those receiving 50 mg twice daily presented with a 34% reduction and those who have taken placebo 26% (p<0.01). The potential side effects of liver damage and carcinogenesis in animals are thought to be related to the pyrrolizidine alkaloids of butterbur, which were removed in the commercially available presentations. Therefore, the tolerability was excellent although it is contraindicated during pregnancy and lactation [39].

Coenzyme Q10

There has been a recent interest in the role that mitochondria may play in migraine pathogenesis. Clues from magnetic resonance spectroscopy (MRS) [40] studies and DNA analysis [41] suggest that migraine, at least in a subset of individuals, may be the result of mitochondrial impairment. Coenzyme Q10 is a naturally occurring substance and essential element of the mitochondrial electron transport chain [42]. A recent study by Rozen et al. [42] assessed the efficacy of coenzyme Q10 as a preventive treatment for migraine headaches. Thirty-two patients with migraine were treated with coenzyme Q10 at a dose of 150 mg/day. Thirty-one of 32 patients completed the study; 61.3% of patients had a greater than 50% reduction in number of days with migraine headache. The average number of days with migraine during the baseline period was 7.34 and this decreased to 2.95 after 3 months of therapy, which was a statistically significant response (p<0.0001). Mean reduction in migraine frequency after 1 month of treatment was 13.1% and this increased to 55.3% by the end of 3 months. Mean migraine attack frequency was 4.85 during the baseline period and this decreased to 2.81 attacks by the end of the study period, which was a statistically significant response (p<0.001). There were no side effects noted with coenzyme Q10. A recent blinded study showed that 300 mg of coenzyme Q10 was statistically better than placebo in prevention of migraine.

New treatment options

Advances in our understanding of the receptors expressed on trigeminal afferents and the neuropeptides most important in initiating and maintaining the pain of migraine, has led to the development of highly selective receptor targets whose modulation would inhibit the release of these neuropeptides. In this way, the transmission of nociception along peripheral

and central trigeminal pathways would be interrupted and pain would be ameliorated or terminated without the need for or the inherent risks associated with drugs that cause vasoconstriction. Below we briefly review some of these options.

Adenosine has an established antinociceptive effect in humans. Recent findings suggest that the analgesic effect of adenosine may be mediated by the adenosine A1 receptor [43]. The relevance of these findings for human migraine is based on the recent observations that A_1 receptor protein is localised in human trigeminal ganglia and two selective A_1 receptor agonists, GR79236 and GR190178, have been shown to inhibit the peripheral release of CGRP in the cranial circulation as well as at the central trigeminal synapse, thereby preventing activation of central trigeminal neurons [44].

A novel neurotransmitter receptor referred to as opioid receptor-like-1 receptor (ORL1) has been identified. The heptadecapeptide nociceptin/orphanin FQ (N/OFQ – nociceptin) has been identified as the endogenous ligand for the ORL-1 (NOP_1) receptor. However, it does not bind to opioidergic μ-, δ- or κ-receptors [33], nor are the effects of nociceptin antagonised by naloxone [45]. Nociceptin seems to be involved in several biological systems and may play a role in central nociceptive processing [45].

Vanilloid type 1 receptors (VR1) are activated by capsaicin, located on small- and medium-sized neurons that are either unmyelinated C-fibres or thinly myelinated Aδ-fibres, and are present on neurons in the human trigeminal ganglia. VR1 receptor activation may lead to CGRP-induced vasodilation at the trigeminovascular junction, and therefore, the VR1 receptor is potentially a feasible target for the development of anti-migraine compounds [45].

LY293558 is an AMPA/KA receptor antagonist and has been tested for the treatment of migraine and pain. In a multicentre randomised, single-attack study patients received LY293558 1.2 mg/kg iv (n=13), 6 mg subcutaneous sumatriptan (n=15) or placebo (n=16). Of 45 patients who were enrolled in the study, 44 completed it. Two-hour headache response rates were 69% for LY293558 (p=0.017 *vs.* placebo), 86% for sumatriptan 6 mg sc and 25% for placebo [46]. Similar compounds could be developed as preventive agents in migraine therapy.

CGRP is one of several neuropeptides found within the sensory terminals of the trigeminal nerve. Recent data suggests that antagonising the effect of CGRP may provide acute relief of migraine headache [47]. Preventive drugs might be developed on the same principle.

Conclusions

The development of new agents for the prevention of migraine has lagged behind the advances in acute therapy that occurred with the introduction of the triptans. However, new and emerging options, some of them studied in extensive well controlled clinical trials, give hope for the development of future preventive agents. We are clearly in better shape with regard to migraine prevention in comparison to a few years ago. It can be expected that modern neuroscience will provide more efficacious tolerable and safe preventive medications for patients with migraine.

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